

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Currently amended) A method of determining the specific residues binding to a target of interest, such residues being within a known parent polypeptide that binds to the target of interest, comprising the steps of:

(a) providing a known parent polypeptide with a known primary structure, such primary structure consisting of  $n$  residues where  $n$  is 3 to about 20 amino acid residues, which parent polypeptide binds to a target of interest;

(b) constructing a first peptide of the formula  $R_1-Z-R_2$ ,

wherein

$R_1$  comprises from 2 to  $n$  residues, such residues the same as residues in the parent polypeptide and in the same order as residues in the parent polypeptide primary structure, provided that any proline residue in the two residue positions immediately adjacent the amino-terminus side of C is substituted with glycine, alanine, serine, amino isobutyric acid, 1-amino,1-cyclopentane carboxylic acid, or dehydroalanine, and any cysteine residue in  $R_1$  is S-protected or substituted with glycine, alanine, serine, amino isobutyric acid, 1-amino,1-cyclopentane carboxylic acid, or dehydroalanine;

$Z$  is an amino acid residue providing both a nitrogen atom (N) and a sulfur atom (S) for metal ion complexation;

$R_2$  comprises from 0 to  $n - 2$  residues, such residues the same as residues in the parent polypeptide and in the same order as residues in the parent polypeptide primary structure, provided that any cysteine residue is S-protected or substituted with glycine, alanine, serine, amino isobutyric acid, 1-amino,1-cyclopentane carboxylic acid, or dehydroalanine, and forming with  $R_1$  a sequence in the same order as in the parent polypeptide primary structure with  $Z$  either inserted between two adjacent residues corresponding to two adjacent residues in such primary structure or substituting for a single residue corresponding to a single residue in such primary structure, and wherein the residues comprising  $R_1-Z-R_2$  are equal to either  $n$  or  $n + 1$ ;

- (c) complexing the first peptide of the formula R<sub>1</sub>-Z-R<sub>2</sub> to a rhenium (Re) or technetium (Tc) metal ion, thereby forming a first R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide;
- (d) screening the first R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide for binding to the target of interest;
- (e) repeating steps (b) through (d), wherein the resulting R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide differs in at least either R<sub>1</sub> or R<sub>2</sub>; and
- (f) selecting the R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide exhibiting decreased binding to the target of interest, whereby at least one residue of the sequence binding to the metal ion of such R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide comprises the identification of the specific residues of the parent polypeptide binding to the target of interest.

2. (Original) The method of claim 1 wherein Z is an L- or D-3-mercaptoproto amino acid.

3. (Currently amended.) The method of claim 2 wherein the L- or D-3-mercaptoproto amino acid is L- or D-cysteine, L- or D-penicillamine, or 3-mercaptoproto phenylalanine, or a homolog of any of the foregoing.

4. (Canceled)

5. (Original) The method of claim 1 wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

6. (Original) The method of claim 1 wherein screening for binding to the target of interest comprises competing a known binding partner for binding to the target of interest with the R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide.

7. (Original) The method of claim 6 wherein the known binding partner is the parent polypeptide.

8. (Original) The method of claim 1 wherein screening for binding to the target of interest comprises a functional assay.

9. (Original) The method of claim 1 wherein the target of interest is a biological receptor capable of transmitting a signal, and screening further comprises determining whether the R<sub>1</sub>-Z-R<sub>2</sub> metallopeptide induces decreased transmission of the signal.

10. (Currently amended) A method of determining the specific residues binding to a target of interest within a known primary sequence parent polypeptide that binds to the target of interest, comprising the steps of:

(a) providing a parent polypeptide with a known primary sequence consisting of from three to about twenty amino acid residues;

(b) making a series of peptides, wherein each peptide in the series includes the known primary sequence of the parent polypeptide and a single inserted L- or D-3-mercaptopo amino acid residue, with the single L- or D-3-mercaptopo amino acid inserted for each peptide at each position along the primary sequence from the position between the second and third residues from the N-terminus through the C-terminus position;

(c) complexing each peptide in the series with a rhenium or technetium metal ion to form a series of metallopeptides;

(d) determining the binding of each metallopeptide of the series of metallopeptides to the target of interest; and

(e) selecting the metallopeptide or metallopeptides of the series exhibiting decreased binding to the target of interest; and

(f) identifying the amino acid residues involved in rhenium or technetium metal ion complexation other than the inserted L- or D-3-mercaptopo amino acid residue;  
whereby at least one of the identified amino acid residues involved in rhenium or technetium metal ion complexation comprises one or more of the specific residues binding to a target of interest within the known primary sequence parent polypeptide that binds to the target of interest.

11. (Canceled)

12. (Original) The method of claim 10, wherein any L- or D-3-mercaptopo amino acid residue in the series of peptides other than the single inserted L- or D-3-mercaptopo amino acid residue further comprises a sulfur protecting group, whereby the sulfur therein cannot complex a metal ion.

13. (Currently amended) The method of claim 10, wherein any L- or D-3-mercaptopo amino acid residue in the series of peptides other than the single inserted L- or D-3-mercaptopo amino acid residue is substituted with a homolog glycine, alanine, serine, amino isobutyric acid, 1-amino.1-cyclopentane carboxylic acid, or dehydroalanine.

14. (Currently amended) The method of claim 10, wherein for any peptide in the series containing a proline residue as either of the two residues on the immediately adjacent N-terminus side of the single inserted L- or D-3-mercaptopo amino acid residue, the proline residue is substituted with a homolog glycine, alanine, serine, amino isobutyric acid, 1-amino.1-cyclopentane carboxylic acid, or dehydroalanine.

15. (Currently amended) The method of claim 10, wherein the L- or D-3-mercaptopo amino acid is L- or D-cysteine, L- or D-penicillamine, or 3-mercaptopo phenylalanine, or a homolog of any of the foregoing.

16. (Canceled)

17. (Canceled)

18. (Original) The method of claim 10 wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

19. (Original) The method of claim 10, wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises competing a known binding partner for binding to the target of interest with each metallopeptide.

20. (Original) The method of claim 10, wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises a functional assay.

21. (Original) The method of claim 10, wherein the target of interest is a biological receptor capable of transmitting a signal, and wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises determining whether each metallopeptide induces decreased transmission of the signal.

22. (Currently amended) A method of determining the specific residues binding to a target of interest within a known primary sequence parent polypeptide that binds to the target of interest, comprising the steps of:

(a) providing a parent polypeptide with a known primary sequence consisting of from three to about twenty amino acid residues;

(b) making a series of peptides, wherein each peptide in the series includes the known primary sequence of the parent polypeptide with a single substitution, the single substituent consisting of an L- or D-3-mercaptoproline amino acid residue substituted at each position along the primary sequence from the third residue from the N-terminus through the C-terminus residue;

(c) complexing each peptide in the series with a rhenium or technetium metal ion to form a series of metallopeptides;

(d) determining the binding of each metallopeptide of the series of metallopeptides to the target of interest; and,

(e) selecting the metallopeptide or metallopeptides of the series exhibiting decreased binding to the target of interest; and

(f) identifying the amino acid residues involved in rhenium or technetium

metal ion complexation;

whereby at least one of the identified amino acid residues involved in rhenium or technetium metal ion complexation or the amino acid residue substituted with an L- or D-3-mercaptopo amino acid residue comprises one or more of the specific residues binding to a target of interest within the known primary sequence parent polypeptide that binds to the target of interest.

23. (Canceled)

24. (Original) The method of claim 22, wherein any L- or D-3-mercaptopo amino acid residue in the series of peptides other than the single substituent L- or D-3-mercaptopo amino acid residue further comprises a sulfur protecting group, whereby the sulfur therein cannot complex a metal ion.

25. (Currently amended) The method of claim 22, wherein any L- or D-3-mercaptopo amino acid residue in the series of peptides other than the single substituent L- or D-3-mercaptopo amino acid residue is substituted with a homolog glycine, alanine, serine, amino isobutyric acid, 1-amino.1-cyclopentane carboxylic acid, or dehydroalanine.

26. (Currently amended) The method of claim 22, wherein for any peptide in the series containing a proline residue as either of the two residues on the immediately adjacent N-terminus side of the single substituent L- or D-3-mercaptopo amino acid residue, the proline residue is substituted with a homolog glycine, alanine, serine, amino isobutyric acid, 1-amino.1-cyclopentane carboxylic acid, or dehydroalanine.

27. (Currently amended) The method of claim 22, wherein the L- or D-3-mercaptopo amino acid is L- or D-cysteine, L- or D-penicillamine, or 3-mercaptopo phenylalanine, or a homolog of any of the foregoing.

28. (Canceled)

29. (Canceled)

30. (Original) The method of claim 22, wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

31. (Original) The method of claim 22, wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises competing a known binding partner for binding to the target of interest with each metallopeptide.

32. (Original) The method of claim 22, wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises a functional assay.

33. (Original) The method of claim 22, wherein the target of interest is a biological receptor capable of transmitting a signal, and wherein determining the binding of each metallopeptide of the series of metallopeptides to the target of interest comprises determining whether each metallopeptide induces decreased transmission of the signal.

34. (Withdrawn) A metallopeptide library for determining the specific residues binding to a target of interest within a known primary sequence parent polypeptide of at least five amino acid residues that binds to the target of interest, comprising:

a series of metellapeptides, wherein each metallopeptide within the series includes the known primary sequence of the parent polypeptide and a single inserted L- or D-3-mercaptoproline amino acid residue, with the single L- or D-3-mercaptoproline amino acid inserted for each peptide at each position along the primary sequence from the position between the second and third residues from the N-terminus through the C-terminus position, and a metal ion complexed to the sequence comprising the single inserted L- or D-3-mercaptoproline amino acid and the two residues on the immediately adjacent N-terminus side of the single inserted L- or D-3-mercaptoproline amino acid residue,

wherein any L- or D-3-mercaptoproline residue in the series of peptides other than the single inserted L- or D-3-mercaptoproline residue either further comprises a sulfur protecting group, whereby the sulfur therein cannot complex a metal ion, or a homolog, and further wherein for an metallopeptide in the series containing a proline residue as either of the two residues on the immediately adjacent N-terminus side of the single inserted L- or D-3-mercaptoproline residue, the proline residue is substituted with a homolog.

35. (Withdrawn) The metallopeptide library of claim 34, wherein the inserted L- or D-3-mercaptoproline amino acid is L- or D-cysteine, L- or D-penicillamine, 3-mercaptoproline phenylalanine, or a homolog of any of the foregoing.

36. (Withdrawn) The metallopeptide library of claim 34, wherein metal ion is an ion of V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Re, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu or Gd.

37. (Withdrawn) The metallopeptide library of claim 36, wherein the metal ion is an ion of technetium or rhenium.

38. (Withdrawn) A metallopeptide library for determining the specific residues binding to a target of interest within a known primary sequence parent polypeptide of at least five amino acid residues that binds to the target of interest, comprising:

a series of metellapeptides, wherein each metallopeptide within the series includes the known primary sequence of the parent polypeptide with a single substitution, the single substituent consisting of an L- or D-3-mercaptoproline amino acid residue substituted at each position along the primary sequence from the third residue from the N-terminus through the C-terminus residue, and a metal ion complexed to the sequence comprising the single substituent L- or D-3-mercaptoproline amino acid and the two residues on the immediately adjacent N-terminus side of the single substituent L- or D-3-mercaptoproline amino acid residue,

wherein any L- or D-3-mercaptoproline amino acid residue in the series of peptides other than the single substituent L- or D-3-mercaptoproline amino acid residue either further comprises a

sulfur protecting group, whereby the sulfur therein cannot complex a metal ion, or a homolog, and further wherein for an metallopeptide in the series containing a proline residue as either of the two residues on the immediately adjacent N-terminus side of the single substituent L- or D-3-mercaptoproline amino acid residue, the proline residue is substituted with a homolog.

39. (Withdrawn) The metallopeptide library of claim 38, wherein the substituent L- or D-3-mercaptoproline amino acid is L- or D-cysteine, L- or D-penicillamine, 3-mercaptoproline, or a homolog of any of the foregoing.

40. (Withdrawn) The metallopeptide library of claim 38, wherein metal ion is an ion of V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Re, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu or Gd.

41. (Withdrawn) The metallopeptide library of claim 40, wherein the metal ion is an ion of technetium or rhenium.